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37 C.F.R. § 1.8

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August 16, 2011
Date

Steven L. Highlander

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Malte PETERS *et al.*	Group Art Unit: 1641
Serial No.: 10/589,450	Examiner: Bradley Duffy
Filed: August 11, 2006	Atty. Dkt. No.: MCMT.P0006US
For: ANTI-EPCAMIMMUNOGLOBULINS	Confirmation No.: 5684

DECLARATION OF SABINE KAUBITZSCH UNDER 37 C.F.R. §1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

I, Dr. Sabine Kaubitzsch, do declare that:

1. I am a citizen of Germany residing at Marschall 20a, 83607 Holzkirchen, Germany. I currently hold the position of Medical Director, Clinical Development Department, at Micromet AG, Munich, Germany. In this position, I am responsible for multicenter clinical studies of MT201, also known as adecatumumab, which is a fully human recombinant IgG1 antibody that specifically binds to the epithelial cell adhesion molecule (EpCAM), and which is the subject matter of the above-identified patent application. A copy of my *curriculum vitae* is attached herewith.

2. In particular, I am responsible for an open-label, multicenter Phase 1b dose-escalation study to investigate the safety and tolerability of a combination regimen of adecatumumab and docetaxel in patients with EpCAM-positive relapsed or primary refractory advanced stage breast cancer.

3. Adecatumumab was administered intravenously on a weekly dosing schedule ("qw dosing schedule") or on a three-weekly dosing schedule ("q3w dosing schedule") at 2 different doses each [dose level 1 (DL1) and dose level 2 (DL2)] in combination with docetaxel that is administered on a three-weekly dosing schedule. The respective doses were escalated when 3 patients completed at least 2 administrations of docetaxel and adecatumumab without the occurrence of a dose-limiting toxicity. Patients that responded to study treatment ("responders") were eligible for two further administrations of docetaxel combined with either 2 adecatumumab administrations on the q3w dosing schedule or 6 adecatumumab administrations on the qw dosing schedule. Patients who demonstrated stable disease, partial response or complete remission after 21 weeks of therapy without any unacceptable toxicity and/or treatment interruption of more than 14 days were offered to participate in a follow-up study with adecatumumab single-agent therapy.

4. More specifically, the study lasted 25-33 weeks consisting of a 3 week screening period, a 15 (q3w) – 17 (qw) for non-responders or 21 (q3w) – 23 (qw) for responders and 7 weeks follow-up. The dosing administration schedules were as follows:

- Three-weekly dosing schedule: Adecatumumab was administered 7 times (9 times for responders) beginning with loading doses of 100, 300 or 500 mg/m^2 at Day 0 and Day 7. At Day 21 maintenance doses of 180, 550 or 1,000 mg/m^2 were administered and repeated every 3 weeks for a total of 5 times (7 times for responders). Standard docetaxel (100 mg/m^2) was administered every 3 weeks for a total of 6 times (8 times for responders).

- Weekly dosing schedule: Adecatumumab was administered 18 times (24 times for responders) at doses of 180, 360, 550 or 1,000 mg/m^2 on Day 0 and repeated weekly. Standard docetaxel (100 mg/m^2) was administered every 3 weeks for a total of 6 times (8 times for responders).

5. This study showed that the combination therapy of adecatumumab and docetaxel was safe and feasible and showed comparable toxicity. The incidence of adverse events was higher at the DL2 of both the q3w and qw dosing schedules. The majority (87%) of serious adverse events were related primarily to docetaxel as they matched those adverse events reported for docetaxel. Only a few adverse events were observed during the adecatumumab single-agent therapy follow-up study.

6. In total, 31 evaluable patients were treated in this study. All patients were in an advanced stage of the disease and had received up to 4.6 ± 1.9 previous therapies. The combination of adecatumumab and docetaxel in this study was administered as third- to fourth-line treatment to these patients.

7. Patients on the q3w dosing schedule had an objective response rate according to RECIST of 22% (n = 4/18). Further, 44% (n = 8/18) of the q3w patients had a clinical benefit defined in this protocol as objective response according to RECIST and/or stable disease for at least 24 weeks. This includes 4 of 5 patients with q3w dosing schedule showing stable disease according to RECIST. Moreover, all 4 patients continued treatment with adecatumumab monotherapy in the follow-up study and maintained their status for on average an additional 5 weeks resulting in

a time to progression of 203.5 days on average. Eleven percent (n = 1/9) of patients on the qw dosing schedule experienced a partial response. Even though 33% of the qw dosed patients were assessed as having stable disease according to RECIST, no additional benefit in terms of the clinical benefit rate, *i.e.*, partial response, complete response or stable disease for at least 24 weeks, was noted for this dosing schedule. None of the patients with stable disease continued adecatumumab monotherapy in the follow-up study.

8. Median time to progression within the q3w dosing schedule was 165.5 days (95% confidence interval [confidence limits: CL] from 42 to 176 days). Whereas median time to progression of the qw dosing schedule was distinctively shorter with 83 days (95% CL from 57 to 124 days). Target- and dose-dependent anti-tumor activity and influence of adecatumumab on the time-to-progression as observed in earlier studies was confirmed here in patients with high levels of EpCAM-expression only in the q3w dosing schedule. No correlation between the level of EpCAM expression and the clinical benefit rate could be detected for patients treated with qw adecatumumab.

9. In general, the determination of dosage for a cancer therapeutic requires a balance between efficacy and toxicity. An initial dosing schedule that administers the therapeutic as frequently as possible would be chosen, and if serious toxicity arises, the dosing frequency is reduced until the toxicity is sufficiently reduced in severity. This would normally be expected to reduce efficacy. As such, one of skill in the art would not normally choose a q3w dosing schedule over a qw dosing schedule.

10. Even if one were to choose a q3w dosing schedule over a qw dosing schedule, the former would be expected to exhibit reduced efficacy, albeit with the advantage of reduced (acceptable) toxicity. The data provided above shows just the opposite - an advantage for the q3w dosing schedule over the qw dosing schedule in longer median time to progression of the EpCAM expressing cancer. I consider it quite unexpected and surprising to obtain improved efficacy as a result of a less frequent dosing schedule.

11. Thus, in conclusion, I find a q3w dosing schedule not to be the regimen of choice in general for cancer therapeutics. Moreover, the study described above showed that a q3w dosing schedule provides improved efficacy over the qw dosing schedule while both dosing schedules have comparable safety results, which result was both surprising and unexpected.

12. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of title 18 of the United States Code.

16/AUG/2011
Date

Sabine Kaubitzsch, Ph.D.

CURRICULUM VITAE

PERSONAL DATA

NAME	Sabine Kaubitzsch, PhD

CURRENT POSITION

Since 03/2008	Medical Director	Micromet AG, Munich

EDUCATION

	DATE, PERIOD	
HIGH SCHOOL GRADUATION	1975-1980	Abitur
STUDIES	1980-1985	Biologie (Dipl. Biologist, Karl-Marx-University, Leipzig)
DEGREE TITLE	1985-1990	PhD (Friedrich-Schiller-University, Jena)

PROFESSIONAL EXPERIENCE

DATE, PERIOD	POSITION	COMPANY
1991-06/1996	Sales force	Bristol-Myers-Squibb
07/1996-07/1997	Sales force	SmithKline Beecham
07/1997-01/2001	Medical Marketing Manager Oncology (Hycamtin, Bexxar) -Medical information -Junior product management	"
01/2001-03/2005	Medical Advisor Oncology -GCP, conduct of clinical trials phase I-IV (Hycamtin und Supportive Care)	GlaxoSmithKline
07/2002-09/2003	Secondment in Communications/ Global Commercial Strategy	"
05/2002-03/2005	Senior Medical Advisor - Clinical trials management (project leadership, medical management) - Medical information - Sales force training	"
04/2005-12/2006	Medical Manager Oncology (Tarceva) - Clinical trials management (project leadership, medical management) - Medical information - Sales force training	Hoffmann-La Roche AG
01/2007-03/2008	Clinical Project Leader	Micromet AG
04/2008-04/2009	Associate Medical Director	Micromet AG
Since 04/2009	Medical Director	Micromet AG

MEMBERSHIPS

ORGANIZATION/INSTITUTION	SINCE
NOGGO (Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie)	2004
ABC (Action Bronchialkarzinom)	2005
IASLC (International Association for the Study of Lung Cancer)	2009

August 11th, 2011 Sabine Kaubitzsch

PROFESSIONAL TRAINING

Subject of training	Date of training	Duration (hours/days)	Course conducted by
Basic Knowledge Internal Medicine for sales force	02.01.-28.03.1991	3 months	Sales Force Training College, BMS
Basic Knowledge Oncology	18.01.-05.03.1993	7 weeks	Sales Force Training College, BMS
Professional Product Management	03.-05.05.1999	3 days	Ott Consulting
Professional Product Management – Follow Up	25.07.2000	1 day	Ott Consulting
Essentials of Pharmaceutical Product Management	07.-11.08.2000	5 days	MCE Brussels
Effective International Presentations	13.-14.09.2000	2 days	ZfU Zürich
Art of Project Management	28.-30.11.2001	3 days	Business Management Consultants
Clinical Research Refresher Course	03.-04.12.2001	2 days	GMED, UK
Statistics and Biometrie in Clinical Research	21.11.2001	1 day	Dr. Banik, GSK
International Laws and Guidelines for Clinical Trials	12.07.2001	1 day	Dr. Gsoedl, GSK
Medical Advisor, Monitoring Training	12.-13.11.2001	2 days	GMED, UK
Gameplan – work in a matrix structure	04.12.2002	1 day	Dr. Gsoedl, GSK
Successful Medical Writing	11.-12-06 2002	2 days	FORUM
Gameplan, Global Communications Strategy	10.01.2003	1 day	Kim Brown
GSK Training Seminar Breast and Renal Cancer	05.-06.11.2003	2 days	Prof. Steward, Prof. Cassidy, Prof. Verril

Subject of training	Date of training	Duration (hours/days)	Course conducted by
Market Research	03.03.2004	1 day	Dr. Stockmann, GSK
Pharrma Codex GSK	09.03.2004	1 day	Dr. Rögner, GSK
12.AMG Novelle – Transformation EU Guideline into national law	02.04.2004	1 day	Dr. Sträter
Leading in non-leading positions	07.-08.07.2004	2 days	Euroforum
Medical Marketing for Medical Managers	07.-09.12.2005	3 days	Roche
Development of High-Risk Biologicals	14.11.2008	1 day	Biotech Cluster Development
Drug Induced Liver Injury/early detection and monitoring of Nephrotoxicity/Bridging the Gap between Clinic and Pre-clinical Studies	29.06.-1.07.2010	3 days	INFORMA
Clinical Trials in Germany	16.10.2010	1 day	S. Zeller
Phase I Clinical Trials	15.-16.02.2010	2 days	INFORMA

12/AUG/2011